REMARKS

A Substitute Sequence Listing, as hard copy and CRF, has been submitted to replace the Sequence Listing filed on December 1, 2000. The Substitute Sequence Listing is identical to the previously filed Sequence Listing, with the exception that the numbering of SEQ ID NO:2 has been corrected to correspond with references to SEQ ID NO:2 in the specification.

According to the Substitute Sequence Listing, the leader sequence (first 25 amino acids as described on page 10, lines 25-27), which was previously numbered as amino acids 1 to 25, is renumbered as amino acids –25 to –1 in SEQ ID NO: 2. It is clear from the context of the specification, *e.g.* at pages 10-11, that such renumbering is appropriate. For example, according to the originally filed Sequence Listing, the active site, defined as amino acids 126 to 177 at page 10, lines 28-29 of the specification, erroneously would have included only 3 of the 6 conserved cysteine residues characteristic of the EGF domain. The remaining conserved cysteine residues would have been located within the transmembrane portion (defined in the specification at page 10, lines 29-32, as residues 178 to 204). The notion that the active site would not include the signature motif of the EGF family is entirely inconsistent with the teachings of the specification as a whole, as well as contradictory to what was known in the art regarding the EGF family of proteins. For example, in summarizing the similarities between the known members of the EGF family, Barnard *et al.* state that "[a]ll are synthesized as glycosylated integral membrane precursor proteins with extracellular domains that contain an EGF-like mature peptide sequence." *See* J. Biol. Chem.(1994), Vol. 269(36), at page 22817, left column, lines 6-9 (emphasis added; a copy of this publication was submitted in parent application 08/778,454 as reference AC in the IDS filed August 4, 2000). Likewise, in commenting on the preserved structural patterns of EGF-like proteins compared across species, Prigent *et al.* state that "[h]ydropathy plots indicate a putative membrane spanning domain, with the EGF-related sequences being located on the extracellular side of the membrane." *See* Progress in Growth Factor Research, (1992) Vol. 4, at page 7, lines 19-20 (emphasis added; a copy of this publication was submitted in parent application 08/778,454 with the IDS filed May 16, 1997). Both of these references were publicly available before the priority date of the instant application.

No correct in Spec.

According to the renumbered amino acid sequence of SEQ ID NO:2 in the Substitute Sequence Listing, the active site would include all of the conserved cysteine residues defining the EGF motif. In fact, the active site would exactly correspond to the portion of TGFα-HIII shown in the alignment of Figure 2. Furthermore, the active site would be located entirely in the extracellular portion of the protein.

In addition, using the numbering of the earlier filed Sequence Listing, the transmembrane portion identified in the specification at page 10, lines 29-32, as amino acids 178-204 of SEQ ID NO:2 would not have included the predominantly hydrophobic residues characteristic of a transmembrane domain, but such residues are included using the numbering of the Substitute Sequence Listing filed herewith.

In summary, upon reading the instant specification in the context of the prior art, the skilled artisan would readily recognize the necessity of renumbering SEQ ID NO:2, and that such renumbering does not introduce new matter.

The specification has been amended to correct an obvious editorial error. Specifically, the Brief Description of Figure 2 at page 5, paragraph 4 incorrectly referred to the sequences aligned in Figure 2 as "TGF alpha HIII (top line)" and "TGF alpha-HI (bottom line; SEQ ID NO:3)". It is clear from the labels on Figure 2, as well as from the sequence of the aligned proteins, that the top sequence corresponds to TGFα and the bottom sequence corresponds to TGFα-HIII. In addition, the paragraph has been amended, at line 15, to indicate the portion of TGFα-HIII aligned in Figure 2 (*i.e.*, residues 126 to 177 of SEQ ID NO:2, as amended). The specification has also been amended at page 10, line 26, to reflect the amended amino acid numbering of the putative signal sequence (*i.e.*, residues –25 to –1 of SEQ ID NO:2). These amendments are supported, for example, by Figures 1 and 2, and throughout the specification as filed. The specification has been amended at page 10, line 27, to recite the amino acid range of the full length polypeptide minus the putative signal sequence (*i.e.*, residues 1 to 204 of SEQ ID NO:2, as amended). The recited range "1 to 204" provides antecedent basis for amended claims 26(b) and 40(b), and is supported, for example, by Figure 1 and original claim 6 filed in parent application 08/778,545 ("The isolated polynucleotide of claim 1 wherein said member is (a) and the polypeptide comprises amino acids 1 to 204 of SEQ ID NO:2"). In addition, a typographical error in the word "amino" at page 11, line 1 has been corrected. Finally, the

address of the ATCC depository recited in the specification has been updated to reflect the current address. Therefore, no new matter has been added.

Claims 19 and 26-81 will be pending upon entry of this amendment. Claims 1, 13, 17, 18, 20, 24, and 25 have been cancelled without prejudice or disclaimer. Applicants wish to point out an editorial error in the numbering of claims submitted with the Election of March 6, 2002. In particular, claim numbers 66 and 67 were inadvertantly skipped. Since this error does not interfere with the examination of the pending claims, Applicants propose to leave the claim numbering as filed.

Part (a) of claims 26 and 40 has been amended to replace the phrase "amino acid residues 1 to 229 of SEQ ID NO:2" with the phrase "the full amino acid sequence shown in SEQ ID NO:2". Part (b) of claims 26 and 40 has been amended to replace the amino acid range "26 to 229" with "1 to 204". Support for these amendments is found, for example, in the paragraph bridging pages 10-11 (as amended), as well as in original claim 6 filed in parent application 08/778,545 (claim 6 quoted above). These amendments are necessary to conform with the amended amino acid numbering of SEQ ID NO: 2, in which the first amino acid residue is numbered –25 (see above). Claims 33 and 50 have been amended to recite "the full-length polypeptide lacking a signal sequence" in part (b), and "the full-length polypeptide lacking a signal sequence and transmembrane portion" in part (c). Support for these amendments is found in the specification, for example, in the paragraph bridging pages 10-11; in the paragraph bridging pages 11-12; and at page 15, paragraph 3 through page 16, paragraph 4. New claims 78 to 81, directed to polypeptides comprising the active site of TGFα-HIII, have been added. Support for new claims 78 to 81 is found, for example, at page 10, lines 27-29; in Figure 2; and in the Sequence Listing as originally filed. Claims 32, 39, 49, 59, 63, 69, 73, and 77 have been amended to indicate expression from recombinant cells. This amendment is supported by the specification, for example, at page 99, paragraph 1. Thus, no new matter has been added.

Formal Matters

The Examiner has indicated that the copy of the cited copending application (reference AL listed on the Information Disclosure Statement [IDS] filed March 6, 2002) did not include the claims, and therefore no determination of double-patenting issues has been made (Paper No. 12, page 2, lines 21-23). Applicants re-submit herewith a copy of the

redacted application, including the claims. Applicants respectfully request that the Examiner consider reference AL, including the claims.

The Examiner has also indicated that references AO and AR-AV listed on the IDS of March 6, 2002 have not been considered, "as no statement of relevance has been provided". The cited references are to GenBank database entries disclosing polynucleotide sequences of expressed sequence tags (ESTs). Applicants respectfully point out that only foreign language references must be accompanied by an explanation of the relevance. The following is a quotation from 37 C.F.R 1.98:

> (a) Any information disclosure statement filed under § 1.97 shall include:
>
> > (3)(i) A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from applicant's specification or incorporated therein.

See 37 C.F.R §1.98 (a)(3)(i); underline added. However, references AO and AR-AV listed on the IDS of March 6, 2002 are in the English language. Applicants respectfully request that the Examiner either cite an authority for requesting a statement of relevance or consider the cited ESTs. Since these references have all been presented previously on an IDS, no supplementary IDS or fee is provided herewith. If a fee is required to consider these references, please charge our Deposit Account No. 08-3425 for the appropriate fee.

Claim Objections and Rejections under 35 U.S.C. § 101-Utility

Claims 26-77 have been rejected under 35 U.S.C. § 101 as allegedly not supported by either a specific, substantial and credible asserted utility or a well established utility. Applicants respectfully disagree and traverse the rejection.

The instant application discloses that polynucleotides, polypeptides, and antibodies of the invention are useful in diagnostic applications, which are independent of the proliferative activity of TGFα-HIII. For example, the specification states that

> [t]he present invention also relates to diagnostic assays for detecting altered levels of the polypeptide of the present invention in various tissues since an overexpression of the proteins compared to normal control tissue samples can detect the presence of certain disease conditions such as neoplasia, skin disorders, ocular disorders and inflammation.

See page 113, lines 10-13. Thus, the claimed TGFα-HIII polypeptides are asserted to be useful for raising antibodies useful in the diagnosis of certain disorders, including neoplasia.

Applicants assert that scientific papers may be used to corroborate Applicants' asserted utility. Legal precedent for the use of post-filing date references in this manner can be found in *In re Brana*, where the courts stated:

> The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4.

See, *In re Brana*, 51 F.3d 1560 at 1567 n.19, 34 U.S.P.Q.2D (BNA) 1436 (March 30, 1995). Accordingly, Applicants submit that the asserted diagnostic utilities are supported by an independent third party publication. Applicants refer to International Publication No. WO00/15666 (the '666 publication, submitted as Reference AC in the IDS filed December 1, 2000), published after the priority date of the instant application. The '666 application discloses a polypeptide sequence, referred to as PRO240 (*see* Figure 8 and SEQ ID NO: 17 of the '666 publication), which is identical to the TGFα-HIII polypeptide shown in SEQ ID NO: 2 of the instant application. The '666 application further discloses that the gene encoding PRO240 is amplified in certain cancers, including lung, colon, breast, kidney, lymph node, and testis tumors (*see* WO00/15666, Table 3, column 5 at pages 94-114; and page 142, lines 6-31). The applicants of the '666 application conclude that PRO240 "is highly probable to play a significant role in tumor formation or growth". *See* page 133, lines 28-29 of the '666 publication. Thus, in view of the supporting evidence, one of skill in the art would find credible the assertion that the claimed TGFα-HIII polypeptides could be used in diagnostic applications, including the detection of cancer. Applicants emphasize that such a use is credible, regardless of the proliferative activity of the claimed TGFα-HIII polypeptides.

The instant application also discloses that TGFα-HIII polypeptides have therapeutic utilities, including "to stimulate wound healing to restore normal neurological functioning after trauma or AIDS dementia, to treat ocular disorders, to target certain cells, to treat kidney and liver disorders and, to promote hair follicular development, to stimulate angiogenesis for the treatment of burns, ulcers and corneal incisions and to stimulate embryogenesis". *See* page 4, paragraph 4. Furthermore, antagonists of TGFα-HIII polypeptides (including antibodies) are useful "in the treatment of corneal inflammation,

neoplasia, for example, tumors and cancers and for psoriasis". *See* page 4, paragraph 8. These uses all involve promoting or inhibiting proliferation of specific cell populations. The aortic smooth muscle cell proliferation data presented in Figure 4 of the application support the conclusion that TGFα-HIII polypeptides mediate cell proliferation. In view of these data, the assertion that the polynucleotides, polypeptides, and antibodies of the invention are useful for regulating cell proliferation is credible.

The Examiner has challenged the relevance of the data presented in Figure 4, alleging that

> [t]his assertion would not be considered credible by one skilled in the art because there is insufficient information provided (i.e. how many replicates, what was the actual difference in cell proliferation observed, is such statistically significant), and because, as the specification itself makes clear, such is merely a preliminary result, in that it is not clear what cell type was affected, and therefore the result is a mere invitation to perform further experimentation to elucidate the properties and possible uses of TGFalpha HIII.

See Paper No. 12, page 6, lines 8-13. Applicants respectfully disagree. Contrary to the Examiner's statement, the instant application does not characterize the data presented in Figure 4 as "preliminary". Given the inclusion of well-accepted positive and negative controls, and the indication of within-groups variability (error bars), a skilled biologist would find the data presented in Figure 4 credible. With respect to the number of replicates, and the cell type affected, the specification clearly states that, "[r]eadings from triplicate samples in each assay were tabulated and averaged" (page 269, lines 21-22); and that "the supernatant caused proliferation of AoSMC [aortic smooth muscle cells]" (page 269, line 26; emphasis added).

The data described in Example 53 and presented in Figure 4 provide credible support for the assertion that TGFα-HIII polypeptides promote cell proliferation. Accordingly, one skilled in the art would find credible the assertion that the claimed polypeptides could be used, for example, to promote cell proliferation associated with wound healing, including the treatment of burns, ulcers and corneal incisions. Likewise, one skilled in the art would find credible the assertion that antibodies against TGFα-HIII could be used, for example, to inhibit cell proliferation associated with inflammation, neoplasia, and psoriasis. In addition, the data presented in Figure 4 provides further support for the assertion that polynucleotides, polypeptides, and antibodies of the instant invention

are useful to diagnose cancer.

Knowledge of a biological or pharmacological activity of a compound is beneficial to the public, and "adequate proof of any such activity constitutes a showing of practical utility." *See, Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980). Applicants disclose in the specification the specific, substantial, and credible assertion that TGFα-HIII polypeptides of the present invention are useful to diagnose conditions associated with overexpression of TGFα-HIII, such as cancer, as well as to promote therapeutic cell proliferation, such as in wound healing and angiogenesis. Applicants submit that adequate evidence in support of the asserted diagnostic and therapeutic utilities has been provided, thereby constituting a showing of practical, real world (*i.e.*, substantial) utility.

The Examiner has also alleged that the instant application does not assert a *specific* utility, stating "applicants have presented a laundry list of thousands of medical conditions that *might* somehow, someday be shown to be associated in some way with the protein applicants designate TGFα-HIII." *See* Paper No. 12, page 4, lines 13-16; emphasis in original.

Applicants respectfully disagree and traverse the rejection. Applicants need only make *one* credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. § 101; additional statements of utility, even if not "correct," do not render the claimed invention lacking in utility. *See, e.g., Raytheon v. Roper*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). *See also*, M.P.E.P. § 2107.01 (I) at 2100-29.

Furthermore, Applicants respectfully point out that they are not required to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. *See* M.P.E.P. § 2107.02 (I) at 2100-33 to 2100-34. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility. *See, Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980). Applicants assert that such a reasonable correlation exists between the disclosed activities, *e.g.* aortic smooth muscle cell proliferation, and the asserted utilities, for example, the treatment of cardiovascular disorders and cancer.

The Examiner has also alleged that "the uses based on the expression patterns or activity of TGFα or other EGF family members are not credible." *See* Paper No. 12, page 5, first sentence. Applicants submit that the Examiner's argument is rendered moot by data supporting the asserted utilities, as described above.

The Examiner has further challenged the credibility of the Applicants' basis for utility, stating that "no indication of a degree of homology nor any alignment to such are provided, and a sequence search of the amino acid sequence databases did not reveal any significant homology to such (i.e. none of the 'hits' returned was an alignment with TGFalpha)." *See* Paper No. 12, page 3, lines 15-17. Applicants respectfully direct the Examiner's attention to Figure 2 and the corresponding figure legend (as amended) at page 5 of the specification. Figure 2 shows an alignment between TGFα (top) and TGFα-HIII (bottom), clearly indicating the conserved EGF motif. As stated in the cited chapter by van Zoelen et al. (in Growth Factors and Receptors: A Practical Approach, Oxford University Press, Oxford, 1998) and emphasized by the Examiner in Paper No. 12 (*see* page 5, lines 4-6), the overall degree of amino acid identity can be relatively low between EGF receptor ligands with similar affinity, such as the 40% identity between TGFα and EGF. Proteins with conserved motifs but low overall identity may be overlooked in standard BLAST analyses.

In summary, the pending claims are supported by specific, substantial, credible, and well established utilities. In view of the arguments presented herein, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 26-77 under 35 U.S.C. § 101 for allegedly lacking utility.

Claim Rejections under 35 U.S.C. § 112, first paragraph – Enablement

I. The Examiner has rejected claims 26-77 under 35 U.S.C. § 112, first paragraph, alleging that, "since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility... one skilled in the art clearly would not know how to use the claimed invention." *See* Paper No. 12, page 7, lines 7-10.

Applicants respectfully disagree and traverse the rejection.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, Applicants assert that the instant invention does fulfill the utility requirement of 35 U.S.C. § 101. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection

grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-28. Therefore, because the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

II. The Examiner has rejected claims 40, 50, 64 and 65 as allegedly not enabled for the full scope of the claims. This rejection is directed to claims reciting polypeptides at least 90% identical to SEQ ID NO:2 or to the polypeptide encoded by the deposited cDNA, as well as to claims reciting polypeptides consisting of at least 30 amino acids of SEQ ID NO:2, fused to a heterologous amino acid sequence. The Examiner has alleged that "no specific variants are disclosed, nor is there guidance as to how to make variants which retain biological activity, nor how to use variants which do not retain such activity." *See* Paper No. 12, page 7, lines 19-21.

Applicants respectfully disagree and traverse the rejection. First, Applicants note that the Examiner appears to mischaracterize the claims as encompassing "unspecified variant polynucleotides that hybridize under unspecified conditions and bind to a particular cell". *See* Paper No. 12, page 7, lines 16-17; emphasis added. Applicants wish to clarify that the pending claims are directed to polypeptides, and contain no limitation of hybridizing or binding to a particular cell.

The Examiner has alleged that, in this case, due to the low degree of sequence conservation in the EGF family, "the predictability in the art of altering proteins and retaining function is relatively low." *See*, Paper No. 12 at page 8, lines 3-7. The Examiner has further alleged that undue experimentation would be required to make and use the claimed polypeptide fragments and variants.

Applicants point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the claimed polypeptide and practice *a single* use of the claimed polypeptide without undue experimentation.[1] Thus, Applicants submit that to be fully enabled, the polypeptides of the

[1] The Applicant need show utility for only one disclosed purpose. See, *Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 USPQ 223 (Pat. Off. Bd. App. 1958).

invention do not necessarily have to have biological activity, *e.g.*, promote cell proliferation, but need merely have application in a single use, such as, for example, to raise antibodies useful in the detection of certain disorders, including cancer.

Applicants submit that the specification fully enables one of ordinary skill in the art to routinely make and use the claimed polypeptides, without undue experimentation, and that the predictability of sequence alterations is not low. First, the specification provides ample guidance as to which regions of the TGFα-HIII polypeptide may be altered with a reasonable expectation of success. For example, the specification discloses structural features including the EGF motif domain (*see* Figure 2), signal sequence, transmembrane portion, and soluble portion (*see* page 10, line 19 through page 11, line 3). Furthermore, the specification provides detailed structural analysis of alpha, beta, turn, and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index; and surface probability (*see* Figure 3 and Table I at pages 45-48). Also disclosed are preferred epitopes of the TGFα-HIII polypeptide (for example, *see* page 54, lines 28-30). The skilled worker would be able to use this structural information to design TGFα-HIII polypeptides for diagnostic and therapeutic uses. For example, the structural teachings of the instant application would provide ample guidance for producing polypeptide fragments and variants useful for raising antibodies specific for TGFα-HIII polypeptides. As taught in the specification, such antibodies could be used in diagnostic applications, for example, in the detection of cancer (*see, e.g.,* page 113, paragraph 2); or in therapeutic applications, for example as antagonists (*see, e.g.,* page 177, paragraph 6). The specification further describes methods of raising antibodies using TGFα-HIII polypeptides, including polypeptide fragments and variants (for example, see Epitopes and Antibodies, at pages 49-53, and Methods of Producing Antibodies, at pages 65-74). In addition, the structural teachings of the specification would provide ample guidance for producing polypeptide fragments and variants which regulate cell proliferation. The specification also provides assays, such as the cell proliferation assays described in Example 53 at pages 268-270, that could routinely be used to evaluate the activity of TGFα-HIII polypeptide fragments and variants.

Applicants submit that because of (1) the disclosure and characterization in the specification of the polypeptide sequence corresponding to TGFα-HIII; (2) the availability

of routine techniques for generating antibodies against TGFα-HIII polypeptides and for assaying the ability of an antibody to bind TGFα-HIII polypeptides; (3) the availability of routine techniques for generating TGFα-HIII polypeptide fragments and variants and for assaying cell proliferation activity; (4) the high level of skill in the field of molecular biology and immunology; and (5) the direction and guidance provided by the specification, one skilled in the art could routinely generate the claimed polypeptide fragments and variants and determine whether these polypeptides elicit antibodies against TGFα-HIII polypeptides, or possess TGFα-HIII activity. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of claims 40, 50, 64 and 65 under 35 U.S.C. § 112, first paragraph.

III. The Examiner has also rejected claims 50-59 and 74-77 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. In particular, the Examiner contends that "Applicants must state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent." *See* Paper No. 12, Page 9, lines 10-11.

Applicants note that the statement being required by the Examiner is explicitly made in the specification at page 11, lines 11-12. However, in the interest of facilitating prosecution of the instant application, Applicants' representatives enclose herewith a "Statement Concerning the Deposited cDNA Clone". The rejection is obviated by this statement, and Applicants respectfully request that the rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 112, first paragraph – Written Description

The Examiner has rejected claims 33, 35, 37-39, 50, 52, 55, and 57-59 under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. In particular, the Examiner has stated that "the specification fails to adequately describe what is meant by "mature TGFalpha HIII". *See* Paper No. 12, page 8, lines 24-25.

Applicants respectfully disagree. The skilled artisan would readily recognize the meaning of the term "mature" as used in the pending claims. However, solely in the interest of facilitating the prosecution of the instant application, claims 33 and 50 have been amended to replace "the mature polypeptide" with "the full-length polypeptide lacking a signal sequence". Applicants submit that the amended claims are fully described in the

specification, and respectfully request that the Examiner reconsider and withdraw the rejection of claims 33, 35, 37-39, 50, 52, 55, and 57-59 for alleged lack of written description.

Claim Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

I. Claims 32, 39, 49, 59, 63, 69, 73, and 77 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner has alleged that

> it is not clear what the phrase "expressing the polypeptide of claim X by a cell" indicates; such might read on any possible means of getting a cell to make such a polypeptide, or alternatively might be intended to indicate expression via recombinant DNA technology.

See Paper No. 12, page 9, lines 22-25. Applicants respectfully disagree and traverse the rejection.

Applicants wish to emphasize that the disclosure of the instant application is not limited to TGFα-HIII polypeptides expressed in any single cell type or by any single protocol. To the contrary, the specification describes the expression and isolation of TGFα-HIII polypeptides from a variety of recombinant and non-recombinant cells:

> TGF alpha HIII polypeptides, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells.

See page 99, lines 6-10. Such techniques were well-known in the art at the priority date of the instant application. However, in the interest of facilitating the prosecution of the instant application, claims 32, 39, 49, 59, 63, 69, 73, and 77 have been amended to indicate expression from recombinant cells. Applicants submit that this amendment obviates the rejection, and request that the rejection be withdrawn.

II. Claims 33, 35, 37-39, 50, 52, 55, and 57-59 have also been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite with respect to the term "mature". Applicants respectfully disagree. However, solely in the interest of facilitating the prosecution of the instant application, claims 33 and 50 have been amended to remove the offending term, as discussed above under Claim Rejections under 35 U.S.C. § 112, first paragraph – Written Description. Applicants submit that the instant rejection no longer

applies to the claims as amended, and respectfully request that the Examiner reconsider and withdraw the rejection.

Claim Rejections under 35 U.S.C. § 103(a) – Obviousness

Claims 60-77 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Genbank Accession No. H02975, which discloses an EST sequence made publicly available on June 20, 1995. Applicants respectfully disagree. The cited GenBank record provides neither a polypeptide translation, nor an indication of which translation frame would produce the encoded polypeptide fragment. Furthermore, the cited reference does not identify the encoded protein as a member of the EGF family of proteins, or indicate any functional significance of the encoded protein fragment. Thus, there would have been no motivation to use the cited EST sequence to obtain a polynucleotide sequence encoding the full-length TGFα-HIII polypeptide, or even to express the protein fragment encoded by the EST. However, in the interest of facilitating the allowance of the instant application, a copy of a Declaration under 37 C.F.R. §1.131, executed by the inventor, Ying-Fei Wei and submitted in parent application 08/778,545, is submitted herewith. The Examiner has indicated that this submission would be effective to overcome the cited EST reference in the instant application. Accordingly, Applicants submit herewith a copy of the declaration under 37 C.F.R. §1.131, executed by the inventor, Ying-Fei Wei, which was filed in parent application 08/778,545. Accordingly this rejection has been obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made remarks be entered and made of record in the file history of the instant application. Applicants believe that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to Deposit Account No. 08-3425.

Respectfully submitted,

Dated: 16 August 2002

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KKH/LJH/JS

Docket No.: PF220P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Wei, Ying-Fei

Application No.: 09/726,348 Group Art Unit: 1647

Filed: December 1, 2000 Examiner: Spector, L.

For: Transforming Growth Factor Alpha HIII

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph at page 5, lines 14-19, with the following paragraph:

--Figure 2 is an illustration of comparative amino acid sequence homology between a portion of TGF alpha (top line) and a portion of human TGF alpha-HIII (bottom line; amino acids 126 to 177 of SEQ ID NO:2[SEQ ID NO:3]). Darkened amino acids denote the conserved EGF motif domain which is shown to be conserved in the polypeptide of the present invention. By examining the regions of amino acids shaded and/or boxed, the skilled artisan can readily identify conserved domains between the two polypeptides. These conserved domains are preferred embodiments of the present invention.--

Please replace the paragraph bridging pages 10-11 with the following paragraph:

--The full-length polypeptide of the present invention as set forth in Figure 1 (SEQ ID NO:2) has a putative signal sequence which comprises amino acid 1 through amino acid 25 of Figure 1 (amino acid –25 through amino acid –1 of SEQ ID NO:2) which aids in secretion of the polypeptide from the cell. One embodiment is a polypeptide comprising amino acid 1 to amino acid 204 of SEQ ID NO:2. Amino acid 126 through amino acid 177 of SEQ ID NO:2 represent the active site of the protein of the present invention. Further, amino acid 178 through amino acid 204 represents a putative transmembrane portion which is thought to be necessary to direct the polypeptide to particular target locations for the carrying out of biological functions as hereinafter described. The transmembrane portion

may also be cleaved from the polypeptide such that the putative soluble portion of the polypeptide of the present invention comprises [amiino]amino acid 1 through amino acid 177 of SEQ ID NO:2. The protein exhibits the highest degree of homology to TGF alpha.--

Please replace the paragraph at page 11, lines 4-19, with the following paragraph:

--In accordance with another aspect of the present invention there are provided isolated polynucleotides encoding a mature polypeptide expressed by the DNA contained in ATCC Deposit No. 97342, deposited with the American Type Culture Collection (ATCC), [12301 Park Lawn Drive, Rockville, Maryland 20852, USA] 10801 University Boulevard, Manassas, Virginia 20110-2209, on November 20, 1995. The deposited material is a bluescript plasmid (Stratagene, La Jolla, CA) that contains the full-length TGF alpha HIII cDNA. The deposit has been made under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for purposes of Patent Procedure. The strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent. These deposits are provided merely as convenience to those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112. The sequence of the polynucleotides contained in the deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted. References to "polynucleotides" throughout this specification includes the DNA of the deposit referred to above.--

In the Claims:

Please amend the claims as follows:

26. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) [amino acid residues 1 to 229 of]the full amino acid sequence shown in SEQ ID NO:2;

(b) amino acid residues [26]1 to [229]204 of SEQ ID NO:2; and

(c) amino acid residues 1 to 177 of SEQ ID NO:2.

32. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 26 [by a cell] under conditions that result in the expression of said polypeptide; and
(b) recovering the polypeptide.

33. (Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342;
(b) the amino acid sequence of the [mature] full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342 lacking a signal sequence; and
(c) the amino acid sequence of the [soluble] full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342 lacking a signal sequence and transmembrane portion.

39. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 33 [by a cell] under conditions that result in the expression of said polypeptide; and
(b) recovering the polypeptide.

40. (Amended) An isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of:
(a) [amino acid residues 1 to 229 of]the full amino acid sequence shown in SEQ ID NO:2;
(b) amino acid residues [26]1 to [229]204 of SEQ ID NO:2; and
(c) amino acid residues 1 to 177 of SEQ ID NO:2.
wherein the polypeptide binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

49. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 40 [by a cell] under conditions that result in the expression of said polypeptide; and
(b) recovering the polypeptide.

50. (Amended) An isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of:
(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342;
(b) the amino acid sequence of the [mature] full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342 lacking a signal sequence; and
(c) the amino acid sequence of the [soluble] full-length polypeptide encoded by the cDNA contained in ATCC Deposit No. 97342 lacking a signal sequence and transmembrane portion;
wherein the polypeptide binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

59. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 50 [by a cell] under conditions that result in the expression of said polypeptide; and
(b) recovering the polypeptide.

63. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 60 [by a cell] under conditions that result in the expression of said polypeptide; and
(b) recovering the polypeptide.

69. (Amended) A polypeptide produced by a method comprising:
(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 64 [by a cell] under conditions that result in the expression

of said polypeptide; and

(b) recovering the polypeptide.

73. (Amended) A polypeptide produced by a method comprising:

(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 70 [by a cell] under conditions that result in the expression of said polypeptide; and

(b) recovering the polypeptide.

77. (Amended) A polypeptide produced by a method comprising:

(a) [expressing]culturing a recombinant cell comprising a polynucleotide encoding the polypeptide of claim 74 [by a cell] under conditions that result in the expression of said polypeptide; and

(b) recovering the polypeptide.